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# Can spatial resolution reveal individual differences in the L:M cone ratio?

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ABSTRACT

We measured spatial resolution in the parafovea for targets designed to isolate either the long-wavelength (L) or the middle-wavelength (M) cones. Landolt C optotypes were presented for 100 ms on a calibrated monitor at an eccentricity of 5° to the left or right of fixation. There were large individual differences in the ratio of the resolution obtained with L targets to that obtained with M targets, and we suggest that these differences reflect variations in the relative sampling densities of L and M cones in the parafovea. In Experiment 1, we measured contrast thresholds for targets of varying size. Among 10 unselected observers, there was a threefold variation in the ratio of the contrast thresholds for the smallest targets. In Experiments 2 and 3, we held contrast constant and we varied size, in order to establish the minimal target that could be discriminated for each of the two classes of cone. In Experiment 2, two groups of observers, selected on the basis of their settings on a flicker-photometric test, showed a highly significant difference in the ratio of the M and L acuities on the spatial task. In Experiment 3, female carriers of protan or deutan deficiencies, classified only on the basis of their sons' phenotypes, also showed a large difference in the ratio of their acuities for M and L targets. In all three experiments, there was a strong correlation between the ratio of M and L spatial acuities and a flicker-photometric measure of relative sensitivity to long- and middle-wavelength light.



## 1. Introduction

In 1948 the Dutch physicist Hessel De Vries proposed that human observers differ in the relative numbers of long- (L) to middle-wave (M) cones (De Vries, 1948, 1950). Strong evidence for his hypothesis has since accumulated. In the present study, we ask whether individual differences in the L:M cone ratio reveal themselves in spatial resolution for targets that favor individual classes of cone. De Vries additionally believed that the differences in cone ratios were heritable: Our results support his suggestion, at least for the special case of carriers of color vision deficiency.

The ratio of L to M cones was classically estimated by finding the additive combination of cone fundamentals that best fits the photopic luminosity function derived by flicker photometry (De Vries, 1946); and a ratio close to 2:1 has often been derived for the average observer (e.g. Boynton, 1979; Cicerone & Nerger, 1989; Kremers et al., 2000).

It was on the basis of flicker photometry that De Vries inferred individual differences in L:M ratio in his own small sample. Obtaining flicker photometric measurements from a larger sample of 200 undergraduates, Rushton and Baker (1964) suggested that the L:M ratio varied from 3:1 to 1:3, although they did not explicitly model the photopic luminosity function. Vimal et al. (1989) and Wesner et al. (1991) reconstructed L:M ratios from the relationship of wavelength to the probabilities of detecting neither or one or two dots subtending 1 arcmin and presented to the fovea. For five normal trichromatic observers they found L:M ratios between 1.6 and 7.3; and these values correlated well with values derived by a flicker-photometric method. Combining high-resolution imaging of the retina with retinal densitometry, Hofer et al. (2005) found that the L:M ratio ranged from 1.1:1 to 16.5:1 in a sample of eight subjects. These estimates correlated strongly with those derived by using the electroretinographic analog of flicker photometry.

### 1.1. Variations in peak sensitivities of L and M cones

The wavelengths of peak sensitivity of L and M cones are known to vary within the normal population (Alpern & Moeller, 1977; Dartnall, Bowmaker, & Mollon, 1983; Winderickx et al., 1992); and this variation must complicate any attempt to derive individual L:M ratios from the photopic luminosity function – or from its electroretinographic analog. Bieber, Kraft, and Werner (1998) calculated that variations in the spectral position of the M pigment would have little effect, but variations in the L pigment would significantly affect the estimated ratio. This source of variance will

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necessarily complicate our own measures of individual differences and will be discussed further below.

To attenuate the problem of variations in the spectral positions of the photopigments, Carroll, Neitz, and Neitz (2002) analyzed the opsin gene array in 62 males before reconstructing electroretinographic spectral sensitivities with personalized estimates of the underlying cone sensitivities. They confirmed that the average ratio was close to 2:1 and also confirmed the presence of large individual differences. 80% of their subjects had ratios between 1:1 and 4:1. Personalized estimates of the L-cone sensitivity were used to correct the electroretinographic estimates also in the study by Hofer et al. (2005).

### 1.2. The present experiments

In the present experiments, we measure spatial resolution for brief targets that are calculated to isolate either L or M cones. In two critical ways, our measure is designed to be sensitive to L:M cone ratio:

(i) We measure sensitivity in the parafovea at an eccentricity of 5°. In the fovea, under conditions of normal viewing, spatial resolution is known to be limited primarily by optical factors (Thibos, 1998), but in the parafovea the limit may be set by the sampling density of the cones and thus it is in this retinal region that the relative numerosities of L and M cones might manifest themselves as differences in spatial vision.
(ii) We probe spatial resolution locally, using Landolt C optotypes, rather than an extended grating. If an extended grating is used and if the distribution of L and M cones is random, then there will be patches of retina where a clump of cones of the same type allows the grating to be resolved with a sampling density equal to the overall sampling density of the cone array (Otake, Gowdy, & Cicerone, 2000).

The 2:1 L:M ratio, estimated from flicker photometry and other measures, has always sat uneasily with the traditional evidence that spatial contrast-sensitivity functions and spatial resolution are similar for the long-wavelength and middle-wavelength cones (Cavonius & Estévez, 1975; Green, 1968). It may be relevant that these classical studies used foveal vision and extended gratings. However, Williams (1990) briefly reports a study in which interference fringes were used to by-pass the optics and nevertheless no differences emerged in resolution between the L and M cones.

In the present study, using local targets and parafoveal retina, and assuming the underlying cone sensitivities of the 10-deg Stockman and Sharpe (2000) average observer, we find an average L:M ratio closer to 2:1. In our first experiment, we measured contrast thresholds for differently sized, parafoveal targets that isolated either the long-wavelength or the middle-wavelength cones. In Experiments 2 and 3, we fixed target contrast and varied target size to establish the limit of spatial resolution. In each case, we compare our results with a temporal measure, a variant form of flicker photometry that has been termed 'counterphase modulation photometry'.

## 2. Experiment 1. Methods

### 2.1. Apparatus and stimuli

Stimuli were presented on a 22-inch Mitsubishi color graphics monitor (Diamond Pro 2070). The displays were generated using a VSG 2/3 graphics board (Cambridge Research Systems), allowing a precision of 15 bits per gun. The refresh rate of the screen was 100 Hz and the spatial resolution was 1024 × 768 pixels.

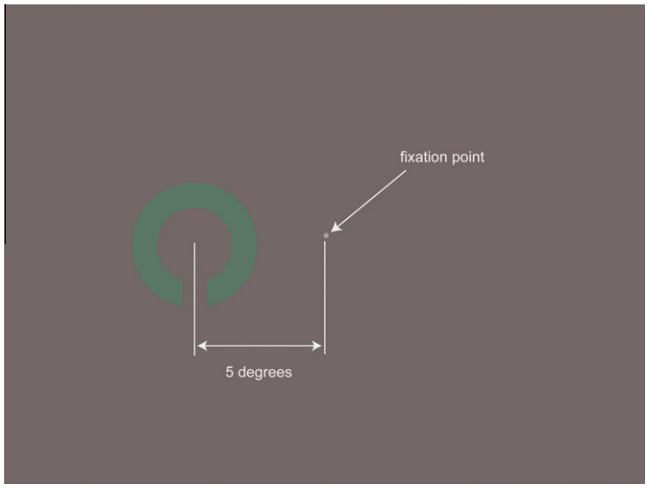


**Fig. 1.** Spatial arrangement of targets used in the experiments.

The test Landolt C's were centered at 5 deg eccentricity and were constructed as in optometric charts: Their gap size and stroke width were 1/5 of the diameter (Fig 1). Viewing was binocular from a distance of 1.14 m. The stimuli were presented on a background that had a CIE luminance of approximately 10 cd/m$^2$ and a chromaticity equivalent to equal-energy white for the 10-deg Stockman-Sharpe observer (Stockman & Sharpe, 2000). A small white fixation point was continuously present in the center of the screen. The monitor output was linearized with an OptiCal photodiode (Cambridge Research Systems) and spectral power distributions were measured with a JETI spectroradiometer.

Target stimuli differed from the neutral background in the excitation of only the L cones or only the M cones of the 10-deg Stockman-Sharpe observer, the excitations of the remaining two cone types being held constant. Cone contrasts were calculated relative to the corresponding L or M values of the background.

### 2.2. Procedure

In separate experimental sessions we measured contrast thresholds for either L-cone increments or M-cone increments. At the beginning of each session, the participant adapted for 1 min to the equal-energy white background. Each session consisted of separate runs corresponding to different diameters of the Landolt C target. On each trial, the test Landolt C appeared randomly either to the left or right from fixation and the observer's task was to report the orientation of the gap – top, bottom, left or right; i.e. a 4-alternative spatial forced choice was required. Feedback was given by auditory signals. The stimulus duration was 100 ms, which was too short to allow participants to move their eyes from fixation towards the target. A double random staircase procedure was used to obtain separate contrast thresholds in the left and the right visual hemifields. After three consecutive correct responses, the corresponding cone contrast was modified so that the difference between the test value and the background value decreased; after one incorrect response, the cone contrast increased. The step size was 10% of the difference between the test and the background. Both staircases continued until at least 15 reversals were accumulated. The first five reversals were discarded and all the subsequent reversals were averaged to give the threshold. The diameter of the Landolt C's varied from 0.9 to 4.4°. At least 5 repetitions for each condition were accumulated on different experimental days.

For each observer we also obtained 10 settings of the OSCAR test (Estévez et al., 1983), a clinical device that employs counterphase modulation photometry to measure relative sensitivity to

green and red light. The test is thought to reflect L:M cone ratios in color-normal observers (Jordan & Mollon, 1997). The participant was seated in front of the monitor used for the Landolt C measurements and the only illumination was from the screen (i.e. with a chromaticity metameric to equal-energy white). The OSCAR device contains two light-emitting diodes, one of wavelength 650 nm and the other of wavelength 560 nm. The outputs of these LEDs are modulated in counterphase at 16 Hz and are mixed within a perspex rod such that the participant sees a flickering orange light. As the participant turns a control knob, the depth of modulation of one LED is increased and the other is decreased; and the task is to find the position of minimum flicker. In contrast to conventional flicker photometry, this 'counterphase modulation photometry' has the advantage that the target remains constant in chromaticity as the control knob is turned and thus chromatic adaptation cannot vary. A discussion of the theoretical basis of the OSCAR test can be found in a paper by Jordan and Mollon (1997). An analogous measure has been used by Kremers et al. (2000) to estimate cone ratios.

### 2.3. Participants

Permission for the study was given by the Psychology Research Ethics Committee of Cambridge University. Ten observers (8 female) participated in the present experiment. All had normal color vision according to the Ishihara Plates and the Cambridge Color Test (Regan, Reffin, & Mollon, 1994). In addition we obtained a single set of measurements from an extreme deuteranomalous male observer. On the anomaloscope this observer has a deutan spectral sensitivity and accepts matches over the full range of red/green ratios except for extreme red values.

## 3. Experiment 1. Results and discussion

In Fig. 2 we plot for each observer the contrast thresholds for different diameters of the Landolt C target. Since there was no significant difference between hemifields (see ANOVA below), we have averaged thresholds for left and right hemifields. For each observer, the left-hand plot shows the thresholds for L and M cones separately and the right-hand plot shows the ratio of the two. We have ordered the observers from low ratio to high at the minimal target sizes. Several features of the results are apparent from these plots:

(i) Thresholds decrease as the diameter of the Landolt C increases. The functions all have a characteristic form: At large gap sizes the thresholds exhibit a flat asymptotic minimum but thresholds rise rapidly at the smallest sizes to the left.
(ii) At small gap sizes, thresholds are usually lower for L-cone stimuli than for M-cone stimuli.
(iii) The ratio of M and L thresholds, as shown in the right-hand panels, typically decreases as target diameter increases. (We give the *threshold ratio* in the format M:L, since higher values of this ratio might be expected to correspond to higher values of the L:M *cone ratio*.)
(iv) There are large individual differences in the ratio of M and L thresholds: for some observers the two thresholds are similar, whereas for others the M-cone threshold is twice that for L-cones. The reliability of these individual differences is apparent from the error bars in the left-hand plots, which represent ±1 SEM based on inter-session variability and are often smaller than the data points.

These observations are reflected in a repeated-measures ANOVA, which was performed on the contrast thresholds with factors: Hemifield (left vs. right), Cone Type (L vs. M), Size of Landolt C and Observer. We included in the ANOVA only those target diameters for which five independent thresholds were available for every observer. The effect of Hemifield was not significant. There were highly significant main effects of Cone Type ($F = 196.5$, $p < 0.0001$), Size of Landolt C ($F = 2275.2$, $p < 0.0001$), and of Observer ($F = 19.4$, $p = 0.001$ after Greenhouse–Geisser correction). Significant interactions were found between Cone Type and Landolt C Size ($F = 88.9$, $p < 0.0001$), between Landolt C Size and Observer ($F = 4.9$, $p = 0.027$ after Greenhouse–Geisser correction) and between Cone Type and Observer ($F = 15.0$, $p = 0.003$ after Greenhouse–Geisser correction).

In Fig. 3, the data of Fig. 2 have been transformed to give spatial contrast sensitivity functions for our two extreme observers (Nos. 1 and 10 in Fig. 2). The reciprocal of the threshold contrast has been taken to give contrast sensitivity. To convert gap size to spatial frequency in cycles per degree of visual angle, we made the conventional assumption (e.g. McAnany & Alexander, 2006) that the relevant frequency corresponds to the reciprocal of twice the width of the critical feature. We recognize that the latter conversion is arbitrary and that the observer may in practice use other frequencies to recognize the orientation of the Landolt C (e.g. Bondarko and Danilova (1997)), but we plot our data on logarithmic scales and we wish to draw attention only to the relative positions of the different functions and to the striking difference between observers. The lines fitted to the data points are exponential functions, as used by Rohaly and Owsley (1993) and McAnany and Alexander (2006) to fit their data for achromatic Sloan letters, gratings and Gabor patches:

$$\mathrm{CSF} = a * f^n * \exp(-p * f),$$

where CSF = contrast sensitivity, $f$ = spatial frequency, $n$ = attenuation at low spatial frequencies, and $a$ and $p$ are vertical and horizontal scaling parameters (McAnany & Alexander, 2006).

The extreme deuteranomalous observer could not detect the M-cone targets at any size or at any available contrast. His L-cone contrast thresholds were lower than the average of the normal values, and he could detect targets of the smallest size. This observer serves as a check on our calibrations.

### 3.1. A measure of L:M cone ratios?

Our proposal (see Section 1) is that the relative numbers of long- and middle-wave cones might be estimated from the spatial resolution for cone-isolating optotypes in the parafovea. In the parafovea, the *absolute* sampling density of the cones is reduced and so this factor is more likely than optical factors to set the limit to resolution. Moreover the use of local optotypes (rather than extended gratings) makes it less likely that observers can exploit an occasional region where cones of the same type are clumped. It is noteworthy (Fig. 2) that our L-cone contrast thresholds for small targets are typically lower than M-cone thresholds, as would be predicted from the cone ratios estimated by other methods. The average ratio for our sample is 1.6.

But why should the superiority of L-cones increase at small gap sizes (Figs. 2 and 3)? It is possible that the nature of the task is different for small and large Landolt C's in the parafovea. When the target is small, the ring as a whole will be well above threshold, and recognition of the position of the gap may be primarily a task of spatial resolution; and thresholds may then be linearly related to the sampling densities of photoreceptors of different types. On the other hand, when the gap is large, all parts of the Landolt ring will be near detection threshold and the task will become one of detecting the presence of increments in three quadrants and the absence of an increment in the fourth quadrant. In this case,

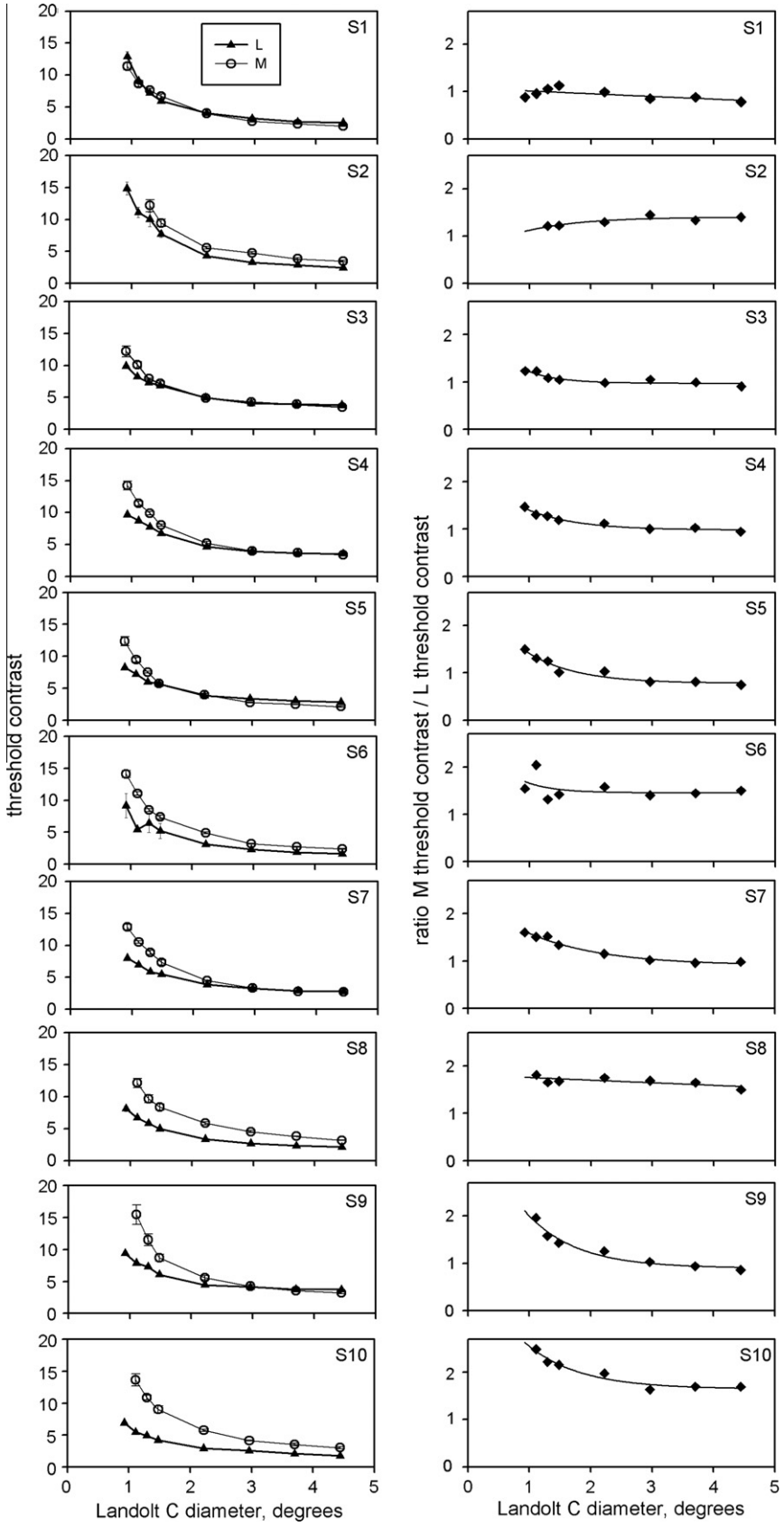


**Fig. 2.** Results from Experiment 1 for 10 observers. The left-hand column shows for each observer the measured contrast thresholds for Landolt C targets as a function of target diameter. The right-hand column shows the ratio of L and M thresholds as a function of target diameter. Observers have been ordered from lowest to highest in terms of their ratio of L to M sensitivity.

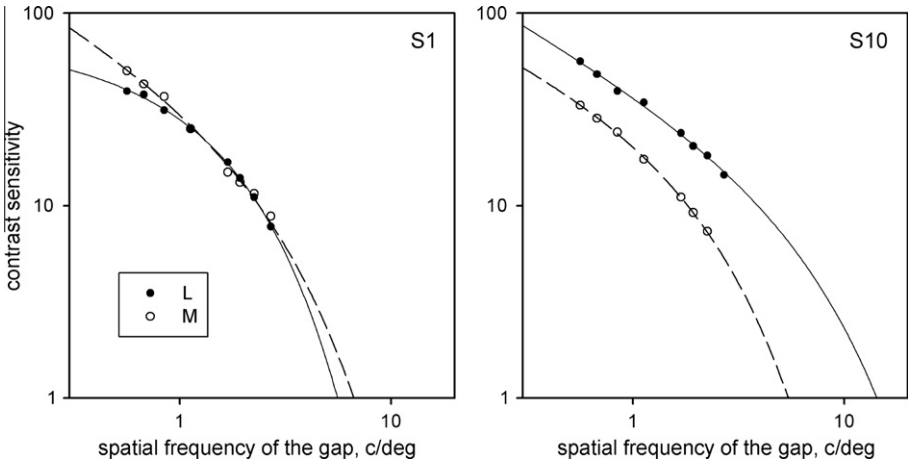


**Fig. 3.** Spatial contrast sensitivities derived from the data of Fig. 2 for the two extreme participants.

thresholds may be related to the square root of the number of photoreceptors contributing to detection.

Different neural channels – perhaps different classes of ganglion cell – may be used to detect small and large gaps, but it is not straightforward to identify these channels as parvocellular and magnocellular respectively. Although the midget ganglion cells (which project to the parvocellular laminae of the lateral geniculate nucleus) have very small receptive fields, it is when the target is large that the observer may use the presence and absence of chromatic signals to solve the task, whereas a conventional assumption would be that larger targets would favor magnocellular channels. When the critical feature is small, the signals of midget ganglion cells may be exploited in a non-chromatic way (Ingling & Martinez, 1983) or detection may depend on a class of ganglion cells that are not chromatically opponent.

### 3.2. Individual differences

Do our present measurements correlate – across individuals – with a more classical psychophysical measure of L:M ratio, the relative flicker-photometric sensitivity to long- and middle-wavelength lights? To derive a measure of relative spatial resolution for L and M cones for each observer of Experiment 1, we fitted the data with arbitrary functions such as those in the left-hand panel of Fig. 2. We took the estimated ratio of sensitivity for targets of 0.185 deg and in Fig. 4 we plot this value against OSCAR test settings for individual observers. Since both variables are subject to experimental error, we used orthogonal regression (Deming regression) to derive the line fitted to the data in this and subsequent scatter plots. Even though our sample in the present experiment is limited to 10 unselected observers, a significant correlation is obtained between the spatial and temporal psychophysical measures of Fig. 4 (Pearson's $r = 0.78$, $p = 0.007$; Spearman's rho = 0.82, $p = 0.004$).

However, it is likely that the strong correlation across observers between spatial and temporal measures depends not only on variations in L:M cone ratio but also on variations in the spectral position of the long-wave photopigment (Bieber, Kraft, & Werner, 1998; see Section 1). Taking the measured spectral power distributions for our L-isolating target and for our background, we calculate that L-cone contrast increases if the L cone is shifted to longer wavelengths and decreases if the L cone is shifted to shorter wavelengths. Such variations in effective contrast might be expected to alter spatial resolution for the L cones in directions that were correlated with the increased or decreased sensitivity to long

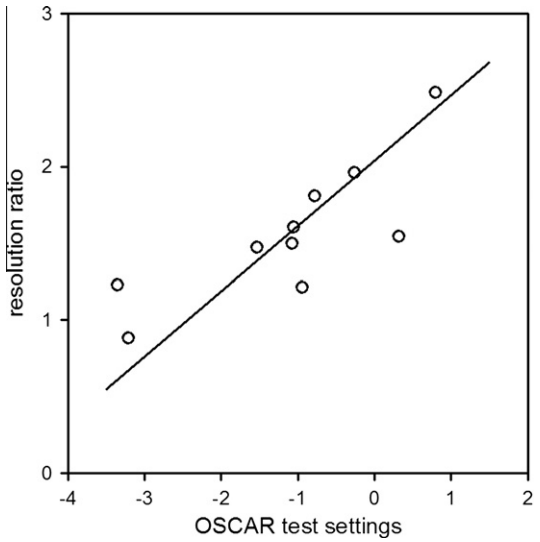


**Fig. 4.** The relationship between our spatial measure (the ratio of sensitivity for L or M targets at small sizes) and our temporal measure (counterphase modulation sensitivity). The spatial measure is derived from the right-hand plots of Fig. 2. Since both the variables in this plot are subject to experimental error, the line fitted to the data is derived by orthogonal ('Deming') regression.

wavelengths that would be apparent from a flicker-photometric measure such as the OSCAR test.

In Experiments 2 and 3, we concentrated on establishing directly the smallest targets that could be resolved with L- and with M-cones in the parafovea; and we recruited populations of observers who might be expected to have unusually high or unusually low L:M cone ratios.

## 4. Experiment 2. Introduction

In the second experiment, we retained the spatial arrangements of Experiment 1 (see Fig. 1) but adopted a different psychophysical procedure: Within each experimental run, we held constant the contrast of the target and we varied the diameter of the target according to the observer's success in identifying the position of the gap. This approach allowed us to avoid the indirect curve-fitting procedure of Experiment 1.

In this experiment, we measured thresholds for decremental as well as incremental targets. There are separate subsystems of midget ganglion cells for increments and decrements (e.g. Dacey, 1993,

1999; Gouras, 1968; Schiller, 2010); and both Dacey (1993) and Kolb and Marshak (2003) have reported that the dendritic fields of ON midget ganglion cells are larger than those of the corresponding OFF cells. If performance in our experiment is determined by the sampling density of different types of cone, then the ratio of long- and middle-wave sensitivity should be similar whether measured with increments or with decrements. A second reason for measuring both increments and decrements is that the chromaticity of an L+ cone-isolating stimulus is similar to that of an M− stimulus and the chromaticity of an M+ stimulus is similar that of an L− stimulus. This provides an interesting control for any effects of chromatic aberration.

The observers in this experiment had taken part a year earlier in an unrelated study (the 'Pergenic' study (Goodbourn et al., 2012)) in which OSCAR settings had been briefly recorded for over 1000 volunteers. Participants were selected for the present study on the basis of having exhibited relatively high or relatively low scores on the test taken the previous year. We recruited participants in the highest 5% and lowest 5% of the original distribution, excluding any who had failed the Ishihara plates. However, the experimenters in the present experiment were blind as to the earlier classification.

## 5. Experiment 2. Methods

### 5.1. Measurement of spatial resolution

The apparatus and the stimuli for the primary measurements were as in Experiment 1, and viewing was binocular from a distance of 1.14 m. In all conditions the Landolt C target (Fig. 1) was presented at a fixed contrast of 0.25. The four types of cone-isolating stimuli (L+, L−, M+, M−) were tested in different blocks of trials. As in Experiment 1, the 100-ms target was centered 5° from fixation, randomly to the right or left, and the observer's task was to report the orientation of the gap. Separate staircases were maintained for the two hemifields. After three consecutive correct responses, the diameter of the target was reduced, and after one incorrect response, it was increased. The step size of the staircase, expressed in terms of the radius of the Landolt C, was 5 pixels; since the proportions of the Landolt C were maintained, this was equivalent to a 2-pixel change (or 2.2 min of arc) in the gap size. Presentations continued until a minimum of 15 reversals had occurred on both staircases. The first five reversals were discarded and all the subsequent reversals were averaged to give the threshold.

### 5.2. Sequence of testing

The participants attended for a single session of 60–90 min and completed a number of clinical vision tests as well as the primary measurements of spatial resolution for cone-isolating targets. They wore their normal correction if necessary. There was a fixed sequence of testing as follows:

1. Visual acuity, measured with a logarithmic letter acuity chart from at a distance of 4 m.
2. Five settings on the OSCAR test.
3. A practice run of the Landolt C test, using only increments.
4. Ishihara plates (10th edition), administered under a Macbeth easel daylight lamp.
5. Rayleigh matches on the Oculus Anomaloscope.
6. A full run of the Landolt C test, with four conditions (L+, L−, M+, M−).
7. A further five settings on the OSCAR test.
8. The Trivector version of the Cambridge Color Test (Regan, Reffin, & Mollon, 1994).
9. A second full run of the Landolt C test.

### 5.3. Participants

There were 20 participants (12 female) aged 17–41. The majority were Cambridge University undergraduates. All had 20/20 acuity or better (using their normal corrections if necessary), and all had normal color vision, as assessed by the Ishihara plates, the Cambridge Color Test and the anomaloscope. One female participant reported a color-deficient father. Since the L:M cone ratio is believed to be lower in those of African descent than in those of Caucasian descent (McMahon et al., 2008), we record that all participants recruited for the present experiment reported four European grandparents; and European ancestry had been confirmed by genomic analysis in the Pergenic study.

### 5.4. Statistical analysis

Since our two sub-groups of participants were originally selected because they fell at the extremes of a normal distribution, it would not be legitimate to assume that their scores would be normally distributed in the present measurements; and so we use non-parametric tests for the statistical analysis.

## 6. Experiment 2. Results and discussion

For each participant we define the 'M:L resolution ratio' as the ratio of the smallest target that can be discriminated by the M cones to the smallest target that can be discriminated by the L cones. Recall that the two subgroups of participants in this study were identified on the basis of OSCAR test settings recorded in a study the previous year. In the box plot of Fig. 5 we show the distributions of resolution ratios for the two groups. A Mann–Whitney test shows that the difference between the two groups is highly significant ($U = 5.5$, $p < 0.001$). It is impressive that clearly different M:L *spatial* resolution ratios are found for participants identified on the basis of a very brief, flicker-photometric test taken many months earlier. This result suggests that we are measuring a basic property of vision and one on which normal observers differ stably over time.

A Wilcoxon signed-ranks test shows no significant difference between the M:L resolution ratios for incremental and decremental targets ($z = -0.885$, $p = .376$). Fig. 6 shows the relationship between the two independent measures: the Spearman rank-order

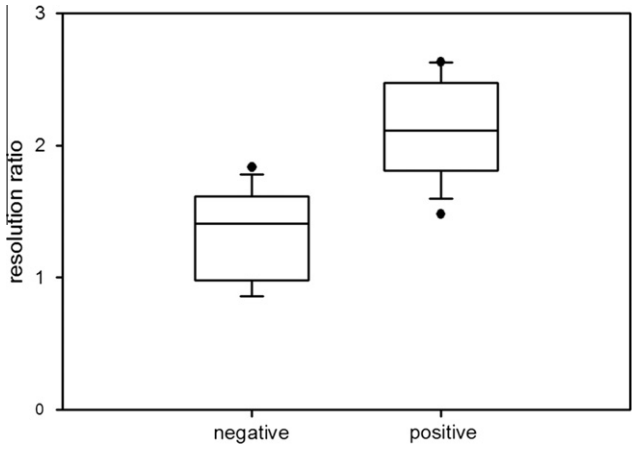


**Fig. 5.** Box plot for the two groups of participants in Experiment 2. The two groups were defined on the basis of the settings that they had made the previous year on the clinical OSCAR test: 'negative' indicates the group of participants whose scores differed in the protan direction from the mean and 'positive' indicates those whose scores differed in the deutan direction. Each box shows the inter-quartile range, and the horizontal line within the box shows the median.

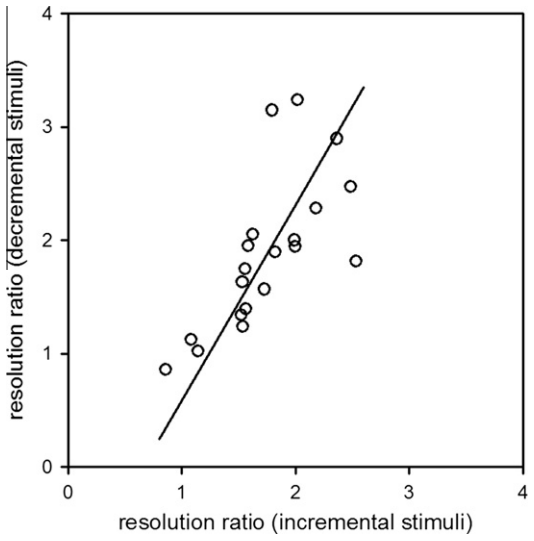


**Fig. 6.** Incremental ratios vs. decremental ratios for all observers.

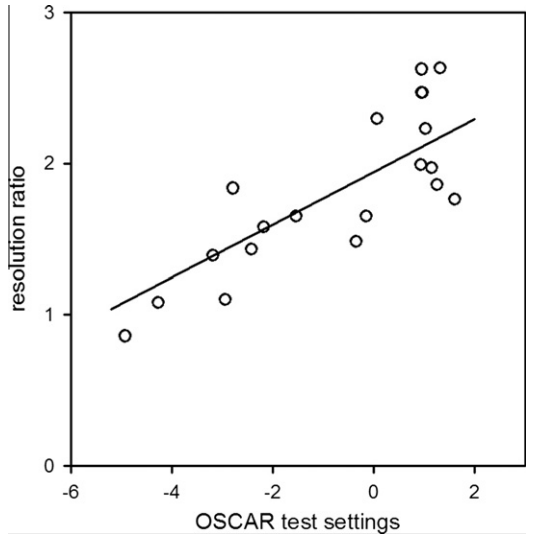


**Fig. 7.** Spatial resolution ratios plotted against OSCAR settings. Here we use the resolution ratios averaged across increments and decrements.

correlation coefficient is 0.808 and is highly significant ($p < .0001$). Thus, whatever is the source of the individual differences that we measure, it appears to be common to both the ON and the OFF neural pathways. Moreover, since the chromaticities of L increments are similar to those for M decrements, and since the chromaticities of M increments are similar to those for L decrements, it is unlikely that the variations we measure in spatial resolution arise simply from individual differences in chromatic aberration.

Our two subgroups of participants were originally selected on the basis of their previous settings on the OSCAR test, obtained very briefly in another project. In the present study, we re-measured their settings on this test. From Fig. 7 it can be seen that these settings obtained by a temporal measure – counterphase modulation photometry – exhibit a strong relationship to spatial resolution ratios. The rank-order correlation is highly significant (Spearman's rho = .785; $p < .0001$).

Each of our observers made three settings on the Oculus anomaloscope. There was a small, non-significant correlation between our spatial measure and the mean Rayleigh match (Spearman's rho = −0.313, $p = .179$). Theoretically, Rayleigh matches have no dependence on the relative numbers of L and M cones but instead reflect variations in the peak sensitivity of the photoreceptors and secondary factors such as the optical density of the photopigment: When the match is made, the quantum catches in the two half-fields must be equated for both L cones and M cones, independently of how many cones there are of each type (Rushton & Baker, 1964). The relatively weak relationship between our spatial resolution ratios and Rayleigh matches, suggests that only part of the variance in the spatial measure derives from variations in the spectral positions of the photopigments.

## 7. Experiment 3. Introduction

On both empirical and theoretical grounds, we can identify one class of observers who almost certainly have abnormal ratios of L and M cones. These are the mothers of sons who exhibit inherited deficiencies of color vision. Such mothers usually have normal match midpoints on the anomaloscope. However, they may reveal themselves by an enlarged matching range on the anomaloscope (De Vries, 1948; Jordan & Mollon, 1993; Pickford, 1944) and more particularly by spectral luminosity functions that are biased in the same direction as are those of their sons. *Schmidt's sign* – a relative insensitivity to long wavelengths in the flicker-photometric settings of protan carriers – was identified early (Schmidt, 1934, 1955) and has often been confirmed (e.g. Adam, 1969; Crone, 1959; Hood et al., 2006; Jordan & Mollon, 1997). De Vries (1948) suggested that deutan carriers, conversely, had higher relative sensitivity to long wavelengths, something that proved to be true statistically (e.g. Adam, 1969; Crone, 1959; Jordan & Mollon, 1997; Swanson, 1991; see also Fig. 11 below).

To explain the abnormal luminosity functions of many protan and deutan heterozygotes, Hessel De Vries suggested that the carriers had abnormal proportions of long- and middle-wave cones. He guessed that the heterozygote carried two 'genetic factors', one that determined the L:M cone ratio in any normal sons she might have, and one that determined the extreme ratio in her color blind sons. Her own ratio, De Vries proposed, would be the mean of these two factors; and he gave examples of families where this appeared to be the case (Table II, De Vries, 1948). What was not available to him in 1948 was theory of Mary Lyon (1961, 1962), who proposed that early in the embryonic development of female mammals either the paternal or the maternal X-chromosome is inactivated in any given cell. Teplitz (1965) showed specifically that inactivation of one X-chromosome occurs in all retinal cones in women. Consider now a heterozygote for protanopia. On average, half her cones will express her normal X-chromosome, making a stochastic choice between long-wave and middle-wave genes (Wang et al., 1999); but those cones that express her other chromosome can yield only middle-wave cones. So her overall proportion of long-wavelength cones will be lower than that characteristic of the average normal. If we take the average normal L:M cone ratio as 2:1 and if we assume that our protan heterozygote inactivates her two X-chromosomes with equal probability, then the estimated value for her L:M ratio will be 1:2 (Hood et al., 2006). Hofer et al. (2005), combining high-resolution retinal imaging with retinal densitometry, found a ratio of 0.37:1 in one protan carrier (whose color vision was clinically normal); this value was lower than any found in their seven male subjects. Carriers of deuteranopia should have more long-wavelength cones than the average normal, but here the L:M ratio will become particularly extreme, owing to the starting bias in favor of long-wave cones: If we take the average ratio as 2:1 and assume that the carrier's two X-chromosomes are expressed with equal probability, then a ratio of 5:1 is expected – a ratio that may be extreme enough to impair the color discrimination of some deutan carriers (Hood et al., 2006).

The expectations for carriers of anomalous trichromacy are similar to those for dichromacy. The protanomalous X-chromosome is thought to lack the gene for a normal long-wave opsin and the deuteranomalous X-chromosome is thought to lack the gene for a normal middle-wave opsin. A complication arises, however, in the interpretation of the two genes still present on the affected X-chromosome. One of these genes is often taken to be the 'normal' gene (e.g. the normal middle-wavelength gene in the case of protanomaly) and the second to be a hybrid or anomalous gene, intermediate in its spectral position between the normal M and the normal L pigments (Deeb, 2006; Nathans et al., 1986). By the hypothesis of Alpern in contrast, both of the X-linked photopigments of the protanomalous observer are drawn from a *population* of normal middle-wave pigments, and both of the X-linked photopigments of the deuteranomalous observer are drawn from a population of normal long-wave pigments (Alpern, 1987; Alpern & Moeller, 1977). In many cases, the distinction between the hypotheses may be metaphysical, since the identities of the critical amino acids in the sequence may be the same in 'anomalous' and 'normal' opsins. For our present purposes we shall assume that heterozygotes for protanomaly have low numbers of long-wave cones and that heterozygotes for deuteranomaly have low numbers of middle-wave cones.

In our third experiment, we therefore recruited carriers of protan and deutan deficiency and measured their spatial resolution for Landolt-C targets designed to favor cones of the L or the M type.

## 8. Experiment 3. Methods

### 8.1. Procedure

The apparatus, the stimuli and the experimental programs were similar to those used in Experiment 2. Viewing distance was 1.5 m. The targets were centered at 5° eccentricity. The contrast of the Landolt C target (Fig. 1) was fixed at 0.25 and target size was varied according to separate staircases for the left and right hemifields. In a practice run, participants completed two blocks of trials with binocular viewing, one for L-cone increments and one for M-cone increments. They then completed four blocks of trials, for L- and M-cone increments and L- and M-cone decrements, using the left eye. This was followed by a second, similar, set of four blocks, using the right eye.

Interleaved with the Landolt-C measurements were three series of 5 settings on the OSCAR test. In addition, Rayleigh matches were obtained on the Oculus anomaloscope; and the Ishihara Test (10th edition) was administered under a Macbeth daylight lamp. Visual acuity was measured with a logarithmic letter acuity chart from a distance of 4 m.

### 8.2. Participants

Obligate carriers were recruited by advertising for mothers of color-deficient sons. Leaflets were distributed to schools, to General Practitioners' surgeries and to optometric practices; and advertisements were placed in newspapers and on social media sites. In the case of each heterozygote mother, we established the phenotype of at least one color-deficient son, using the Ishihara Plates, the Mollon–Reffin 'Minimal' test (Mollon, Astell, & Reffin, 1991), the Oculus anomaloscope and the OSCAR test. We classify the carriers as protan or deutan carriers on the basis of their sons' phenotypes. One mother was herself phenotypically deuteranomalous and was excluded from further analysis. One other deutan carrier was excluded because she gave inconsistent settings on the OSCAR test. In addition to testing the heterozygotes, we also tested (as controls) several women who reported no history of color deficiency in their families. Our final sample of 29 participants comprised 6 protan carriers, 17 deutan carriers and 6 normals. The greater number of deutan carriers than protan reflects the different frequencies of protan and deutan deficiencies in the male population (Pokorny et al., 1979; Vierling, 1935). Participants wore their normal corrections, and all had visual acuity of 20/20 or better, when wearing their corrections. All had Rayleigh matches within the normal range.

## 9. Experiment 3. Results and discussion

For each participant we define the resolution ratio as the ratio of the smallest target that can be discriminated by the M cones to the smallest target that can be discriminated by the L cones. The box plot of Fig. 8 shows the means and distributions of this resolution ratio for our three phenotypic groups: The ratio is highest for deutan heterozygotes and lowest for the protan heterozygotes. It is striking that there are clear differences between the three groups of women even though membership of a given group is determined by the phenotypes of the sons. A one-way Analysis of Variance with Son's Phenotype as the factor showed a highly significant variation among the three groups ($F = 12.4$, $p < .0001$). Post-hoc tests, with Bonferroni correction, showed a significant difference between protan and deutan heterozygotes ($p < .0001$).

We analyzed separately the resolution ratios for left and right eyes and for nasal and temporal hemifields. Wilcoxon signed-ranks tests showed no significant difference between eyes or between nasal and temporal retinae ($z = -1.676$, $p = .094$; $z = -0.011$, $p = .991$). In Fig. 9 we show the relationship across observers of the resolution ratios for left and right eyes (left-hand panel) and for nasal and temporal hemifields (right-hand panel). Spearman's rank-order correlation coefficients were 0.88 and 0.939 respectively ($p < .0001$ in both cases), suggesting that our measurements show good within-session reliability and that the randomness of X-inactivation does not produce large differences between eyes or between hemifields.

In Fig. 10 we plot the relationship between the resolution ratio for incremental stimuli and that for decremental stimuli: the two ratios are very strongly correlated (Spearman's rho = 0.882, $p < .0001$). A Wilcoxon signed-ranks test confirms that there is no significant difference between the incremental and decremental estimates ($z = -0.876$, $p = .381$). Thus, whatever is the source of variance underlying the individual variations in resolution ratio, it appears to be common to both incremental and decremental pathways.

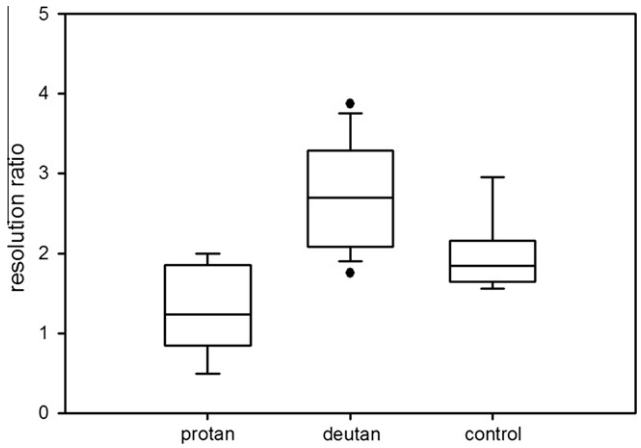


**Fig. 8.** Box plot showing the spatial resolution ratios for three groups of mothers defined in terms of their sons' phenotype, as determined on the anomaloscope. Each box shows the inter-quartile range, and the horizontal line within the box shows the median.

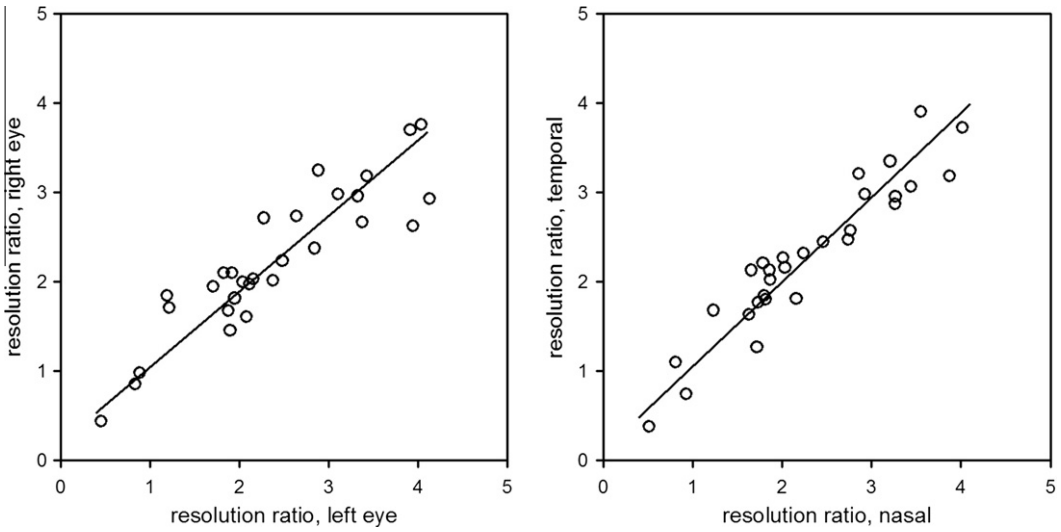


**Fig. 9.** Left-hand panel: Relationship between L:M resolution ratios for left and right eyes for individual observers. Right-hand panel: Relationship between L:M resolution ratios for nasal and temporal hemifields.

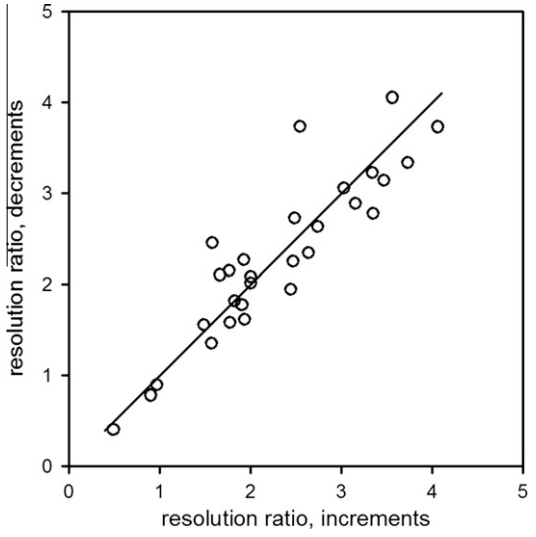


**Fig. 10.** The relationship between the L:M resolution ratios for decrements and for increments.

The left-hand panel of Fig. 11 shows the relationship between our spatial resolution ratio and our temporal measure of L and M cone sensitivity, the OSCAR test. As in Experiments 1 and 2, there is a strong relationship between spatial and temporal measures. The Spearman rank-order correlation in the present case is 0.765 ($p < 0.0001$). Heterozygotes usually have clinically normal color vision, but statistically they reveal themselves by biases in their photopic luminosity functions – and, as we now show, by high or low values of their spatial M:L resolution ratio.

Separate analyses for the three groups of Fig. 11 (left-hand panel) show that there is a significant correlation within the protan group (rho = 1.0, $p < 0.01$) and within the controls (rho = 0.821, $p = 0.023$), but not within the deutan group (rho = 0.422, $p = 0.092$). This pattern probably reflects the classical finding that there is much greater variation in red-green flicker-photometric sensitivity within protan carriers than within deutan carriers (Adam, 1969). A likely theoretical explanation is illustrated in Fig. 12. In the left-hand panel we have used the L- and M-cone sensitivities of the Stockman and Sharpe (2000) 2-deg Observer to construct photopic luminosity functions for subjects with different L:M ratios. (We use a 2-deg Observer because the OSCAR test probes foveal vision). We have made the conventional assumption that the underlying cones contribute additively to the luminosity function in proportion to their relative numbers. The ordinate represents relative sensitivity on an energy basis. It is clear from the left-hand panel of Fig. 12 that the relative sensitivity at long wavelengths changes rapidly with L:M ratio when the L:M ratio is low but much more slowly when L:M ratio is high. In the right-hand panel, we plot, as a function of L:M ratio, the expected ratio of sensitivity at 560 and 650 nm (the primaries of the OSCAR test). Protan carriers are expected to have low L:M ratios and therefore small individual differences in the ratio will express themselves in large variations in relative sensitivity to green and red light; but deutan carriers are expected to have high L:M ratios and even large individual differences in the ratio will lead to only modest variations in sensitivity to green and red light.

The right-hand panel of Fig. 11 shows the relationship between the settings of sons and mothers on the OSCAR test. A Spearman rank-order correlation shows a highly significant relationship between the two (rho = 0.785, $p < .0001$). This result confirms that of Jordan and Mollon (1997).

Taking all the mothers in our sample as a group, there was no significant correlation between spatial resolution ratio and match mid-point on the anomaloscope (Spearman's rho = −0.308, $p = 0.118$) and this remains the case if the controls are excluded (Spearman's rho = −0.289, $p = 0.192$). These results suggest that relatively little variance in spatial resolution ratio derives from variation in the spectral position of the L pigment and that the dominant source of variance is the variation in cone ratio.

We were able briefly to test the protanomalous son of one of our carriers on our spatial resolution test: He was unable to detect the L-cone targets at any diameter, but showed better binocular resolution for M-cone targets than did any of the heterozygous or normal mothers. This serves as a further check on our calibrations.

### 9.1. A note on misreading of the Ishihara plates

Although our heterozygotes all had normal Rayleigh matches, several of them exhibited characteristic minor misreadings of the Ishihara Plates. Jordan and Mollon (1993) recorded that 11 out of

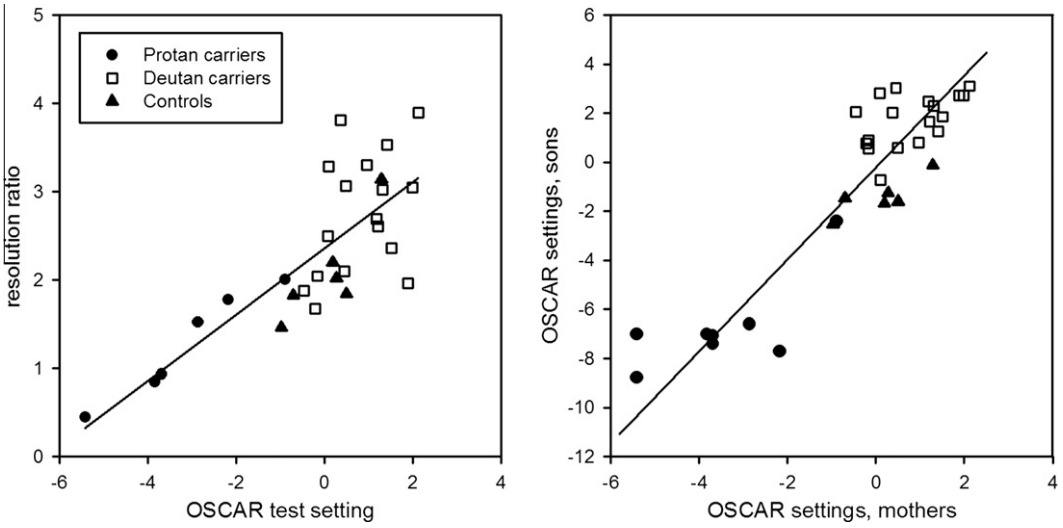


**Fig. 11.** Left-hand panel: Relationship between spatial resolution ratio and flicker photometric settings for individual mothers. Right-hand panel: The relationship between settings on the OSCAR test by mothers and by their sons.

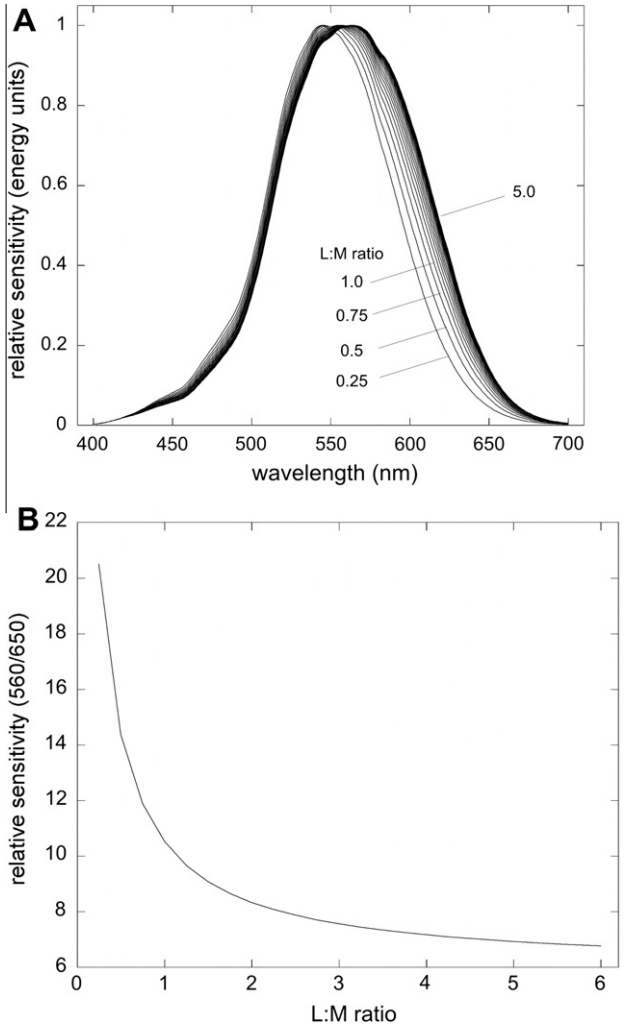


**Fig. 12.** (A) Modeled relative luminosity functions for different L:M ratios, assuming that the underlying photopigments are those of the Stockman and Sharpe (2000) 2-deg observer and that they contribute additively to luminance in proportion to the relative numbers of the different cone types. (B) Change in the relative sensitivity to lights of 560 and 650 nm as a function of the assumed L:M cone ratio.

their 30 heterozygotes (and only 1 out of 12 normals) misread the transformation plate No. 9. In the present sample, 10 of 23 heterozygotes (7/17 deutan, 3/6 protan) misread this plate and no normals did so. Misreading Plate 9 could be regarded as a further sign of the heterozygote.

What is special about Plate 9? It is constructed to offer one reading ('74') to the normal observer and an alternative reading ('21') to color-deficient observers. The two readings depend on the two chromatic subsystems of the early visual system – the phylogenetically ancient subsystem that is thought to compare the signal of the short-wave cones with those of L and M cones, and the phylogenetically younger subsystem that compares the signals of the L and M cones (Dacey & Packer, 2003; Mollon, 2000, 2002). The delicately balanced Plate 9 measures the relative salience of the signals from the two subsystems. For the normal observer, the signal of the younger subsystem is the more salient and he or she perceptually links the green and blue-green elements in the plate. But if the signal of the older subsystem is more salient for the heterozygote, her reading will be guided by the bluish and pinkish elements.

## 10. General discussion

### *10.1. Estimating L:M cone ratio from spatial resolution in the parafovea*

Our procedures differ in two salient ways from those used to derive earlier estimates of spatial resolution for individual cone classes: Firstly, we probe resolution at 5-deg eccentricity, where acuity is likely to be limited by cone sampling density rather than by optical factors. Secondly, we use optotypes that are spatially localized but differ from trial-to-trial in the exact position of their critical feature. Compared to extended gratings, such targets are much less likely to allow observers to exploit patches of retina where there is a clump of L cones or a clump of M cones (Otake, Gowdy, & Cicerone, 2000).

When we use cone-isolating stimuli of this kind, we systematically find that the average sensitivity or resolution is higher for long-wave cones than for middle-wave. Thus, in Experiment 1 only one of our 10 observers had a higher contrast sensitivity for M than for L at the smallest target sizes. In our second experiment, even the group of observers who were chosen to be relatively insensitive

to long wavelengths were on average able to resolve smaller L-cone targets than M-cone targets. In our third experiment, our control observers had an average resolution ratio of 2.08.

Our measure is psychophysical and does not directly reveal the numbers of long- and middle-wave cones in the retina. On the simplest assumption, however, the limit of spatial resolution for our targets is likely to be linearly related to the sampling density of the cone class that is isolated – or to the sampling density of the midget bipolar cells that carry its signals. Since our targets are of relative high contrast and since the primary measure is spatial resolution, we believe that our results are less likely to be affected by differences in L and M gain than are flicker photometric measures. Certainly, our psychophysical results are compatible with the more direct evidence – from retinal imaging (Hofer et al., 2005) and from microspectrophotometry (Bowmaker, Parry, & Mollon, 2003) – that the average human retina contains L and M cones in a ratio of approximately 2:1.

### 10.2. Individual differences

Our experiments suggest that color-normal observers vary by a factor of at least three in the ratio of the smallest target they can resolve with M cones to the smallest they can resolve with L cones. The ranges were 1.1–2.63 (Experiment 1; unselected normal observers), 0.86–2.63 (Experiment 2; observers selected for extreme OSCAR settings) and 0.45–3.90 (Experiment 3; heterozygotes for color deficiency). From our present total sample of 59 observers, none has emerged with a grossly skewed ratio.

This spatial resolution ratio proves repeatedly to correlate with a temporal measure of relative sensitivity to green and red lights. We appear to be measuring a reliable and stable property in which people differ. Our hypothesis is that much of the variance in this perceptual characteristic derives from underlying variations in the relative numbers of long- and middle-wave cones. It would be instructive to test the hypothesis by retinal imaging of subjects who differ on our spatial task.

It is likely that some of the variance in our spatial measure does derive from variation in the spectral position of the long-wave photopigment (Bieber, Kraft, & Werner, 1998). However, this factor is unlikely to be of major importance in our third experiment, where the participants (heterozygotes for color deficiency) are theoretically required to have abnormal L:M ratios and where the large differences in spatial resolution ratio proved to have little relationship with Rayleigh matches. In this context, it is worth noting that hybrid pigments are intermediate in spectral position between 'normal' L and M pigments (Asenjo, Rim, & Oprian, 1994), and so the presence of such pigments within our population of deutan carriers would be expected to act in a direction opposite to the effect of relative cone numbers.

Variation in the spectral position of the long-wave photopigment is unlikely to affect our primary conclusion that the *average* L:M ratio is closer to 2:1 than to unity. The average parafoveal spectral sensitivity of the L photopigment in our population of observers is likely to be close to that of the Stockman and Sharpe (2000) 10-deg Observer, since Stockman and Sharpe based their derivation on the color-matching functions of Stiles and Burch (1959), which were obtained from a British population.

### 10.3. Do the sampling densities of subtypes of midget ganglion cell follow those of the corresponding cones?

Rossi and Roorda (2010), discussing acuity for achromatic targets, have suggested that the sampling density of midget ganglion cells in the parafovea may be poorer than that of the cones themselves and thus may set the limit to spatial resolution. Our own measurements are made at an eccentricity of 5°, close to the limit of the region where midget ganglion cells draw their center input from a single cone (Dacey, 1993) – and of course there may be individual differences in the actual eccentricity at which convergence starts to increase. If indeed parafoveal resolution is limited by the mosaic of midget ganglion cells, will our results still reveal variations in L:M cone ratios? To answer this question, we need to consider other questions about how the subtypes of midget ganglion cell gain their specificity.

There is a long-standing debate as to whether the surrounds of midget ganglion cells draw inputs from only one class of cone (the type opposite to that of the cone that provides the center input) or whether the surround inputs are drawn promiscuously from L and M cones (e.g. Lee et al., 2012; Lennie, Haake, & Williams, 1991; Martin et al., 2001; Reid & Shapley, 1992). Lying behind this question is the question of whether the identity of an L or an M cone lies only in its spectral sensitivity (itself determined stochastically by the binding of the locus control region to a promoter site in the opsin gene array); in this case any specificity of post-receptoral connections would depend on Hebbian learning. Alternatively, L and M cones may carry labels that allow them to identify themselves to post-receptoral neurons. One possible such label could be amino acid differences in the extracellular loops of the opsin itself, embedded in the membrane of the inner segments of the cones (Mollon, 1997).

However, some related questions have seldom been raised. Given that there are large individual variations in the L:M ratio, are the L-ON and L-OFF subtypes and the M-ON and M-OFF subtypes of midget ganglion cell present in the numbers appropriate to the individual? Is there a genetic mechanism to achieve this matching or do the midget ganglion cells gain their own specificity only by the identity of the cone from which they draw their center input? In either case, the results of Dacey (1993) suggest that there is only a single mosaic of midget ganglion cells, without overlap of dendritic fields, and this implies that there must be a matching in L:M ratio between cones and midget ganglion cells. Our own results are consistent with this position, in so far as we find a strong correlation between our spatial measure and our flicker-photometric measure (Figs. 4, 7 and 11) and we find a strong correlation (Figs. 6 and 10) between the estimated L:M ratios for incremental and for decremental targets, which are likely to be detected by independent mosaics of midget ganglion cell.

In sum, we believe our spatial ratios reflect individual differences in L:M cone ratio, even if this relationship arises because the proportions of subtypes of midget ganglion cell follow the proportions of the two types of cone.

### 10.4. Heterozygotes for color vision deficiency

It has been known for some time that carriers of protan and deutan color deficiency, though they may have clinically normal color vision, have statistically different spectral luminosity functions. We have now shown that they also can be differentiated by their spatial resolution for targets that isolate long-wave or middle-wave cones. We suggest that this is almost certainly because protan carriers have unusually low, and deutan carriers have unusually high, proportions of long-wave cones.

Since the human eye exhibits longitudinal chromatic aberration and cannot be optimally focused for L and M cones at the same time, *achromatic* visual resolution may be improved when it depends on a single class of cones, as has been proposed in the case of some dichromats (Jagle et al., 2006). In so far as deutan heterozygotes have a preponderance of one type of cone, we might predict that they would enjoy superior acuity for achromatic targets.

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